New Strategies for the Conduct of Clinical Trials in Pediatric Pulmonary Arterial Hypertension

Ollivier, Cecile; Sun, Haihao; Amchin, Wayne; Beghetti, Maurice; Berger, Rolf M. F.; Breitenstein, Stefanie; Garnett, Christine; Gullberg, Ninna; Hassel, Patrik; Ivy, Dunbar

Published in:
Journal of the American Heart Association

DOI:
10.1161/JAHA.118.011306

Publication date:
2019

SPECIAL REPORT

New Strategies for the Conduct of Clinical Trials in Pediatric Pulmonary Arterial Hypertension: Outcome of a Multistakeholder Meeting With Patients, Academia, Industry, and Regulators, Held at the European Medicines Agency on Monday, June 12, 2017

Cécile Ollivier, MS; Haihao Sun, MD, PhD; Wayne Amchin, RAC; Maurice Beghetti, MD; Rolf M. F. Berger, MD, PhD; Stefanie Breitenstein, MD; Christine Garnett, PharmD; Ninna Gullberg, MD, PhD; Patrik Hassel; Dunbar Ivy, MD; Steven M. Kawut, MD; Agnes Klein, MD, DPH; Catherine Lesage, MD; Marek Migdal, MD, PhD; Barbara Nije; Michal Odermarsky, MD, PhD; James Strait, MD; Pieter A. de Graeff, MD, PhD; Norman Stockbridge, MD, PhD

The Pediatric Regulation (EC) 1901/2006 in the European Union (EU) and the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act in the United States aim to ensure that medicines for use in children are of high quality, are ethically researched, and are authorized appropriately. Such an assessment requires clinically robust and relevant data. However, the conduct of pediatric clinical trials has proved difficult because of the rarity of the diseases and gaps in knowledge in younger populations, leading to a general concern internationally that, depending on the disease and age of the child, 50% to 80% of children are still treated off label.[1–3] Over the years, this gap in available evidence has led to serious unintended harms. For example, the off-label pediatric use of paroxetine was associated with an increased risk of suicidal ideation and hostility, resulting in warnings by regulators that the medicine should not be used in children and adolescents.[4] In addition, local differences related to regulatory requirements, operational practicalities, standards of care, or cultural expectations are creating hurdles to conduct multiregional pediatric drug studies and develop pediatric clinical trials networks required when developing drugs for rare diseases.

Many efforts have been taken among the regulatory agencies in recent years to achieve global regulatory harmonization, which have been helpful to mitigate these challenges in other areas.[5,6] Over the past 3 years, international experts convened to revise the ICH (International Council for Harmonisation) E11 guideline on clinical investigations of medicinal products in pediatric populations to harmonize approaches to pediatric extrapolation, striving to reduce substantial differences between regions in the acceptance of data for global pediatric medicine development programs.[7,8] In addition, there are other activities aiming at a more targeted harmonization at the product or therapeutic level. For example, there are monthly teleconferences among the US Food and Drug Administration, European Medicines Agency, Health Canada, Pharmaceuticals and Medical Devices Agency in Japan, and Therapeutic Goods Administration in Australia to exchange evolving science and discuss the current regulatory approaches for specific product applications in pediatrics.[9] We have harmonized some regulatory approaches for certain pediatric indications, such as pediatric inflammatory bowel disease and Gaucher disease.[5,6]

These concerns and challenges apply also to the treatment of children with pulmonary arterial hypertension (PAH). Pediatric PAH is a rare and complex condition associated with diverse cardiac, pulmonary, and systemic diseases, with significant morbidity and mortality. It shares some similarities

From the European Medicines Agency, London, United Kingdom (C.O., N.G.); Food and Drug Administration, Silver Spring, MD (H.S., W.A., C.G., N.S.); Pediatric Cardiology Unit, Centre Universitaire de Cardiologie et Chirurgie Cardiaque Pédiatrique, University Hospitals of Geneva, City of Geneva, Switzerland (M.B.); Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, the Netherlands (R.M.F.B.); Bayer AG, Pharmaceuticals, Research and Development, Wuppertal, Germany (S.B.); PH Sweden, Göteborg, Sweden (P.H.); Heart Institute, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO (D.I.); Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (S.M.K.); Health Canada, Ottawa, Ontario, Canada (A.K., B.N.); Actelion Pharmaceuticals Ltd, Allscwil, Switzerland (C.L.); Childrens Memorial Health Institute, Warsaw, Poland (M.M.); Department of Paediatric Cardiology, Paediatric Heart Center, Lund University and Skåne University Hospital, Lund, Sweden (M.O.); MSD, Lucerne, Switzerland (J.S.); and Medicines Evaluation Board, Utrecht, the Netherlands (P.A.d.G.).

An accompanying Data S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011306

Correspondence to: Cecile Ollivier, MS, European Medicines Agency, 30 Churchill Place, E14 5EU, London, United Kingdom. E-mail: ollivierces@gmail.com

J Am Heart Assoc. 2019;8:e011306. DOI: 10.1161/JAHA.118.011306.

with adult PAH, but there are important known differences in vascular function, fetal origins of disease, growth and development, genetics, natural history, underlying disease, responses of the right ventricle, responsiveness to PAH-specific therapies, and gaps in knowledge, particularly in the youngest age groups.[10]

Because of the limitations in conducting pediatric studies, therapeutic strategies used for adult PAH have not been studied sufficiently in children to allow the definition of potential toxicities or optimal dosing. Hence, the lack of randomized clinical trials in pediatrics makes it difficult to deliver strong guidelines. On the basis of uncontrolled studies and one randomized controlled trial for sildenafil, STARTS-1 (Sildenafil in Treatment-Naïve Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension), and experts' consensus, recommendations for extrapolating a pharmacological treatment algorithm to pediatric PAH were made at the fifth World Symposium for Pulmonary Hypertension held in Nice, France, in 2013.[11]

Therefore, the European Medicines Agency, the US Food and Drug Administration, and Health Canada coorganized a workshop[12] to discuss the requirements for the development of medicines for pediatric PAH that could address the high unmet medical needs of children.

This report summarizes the main ideas and solutions proposed during the meeting. Ultimately, the goal is to provide a framework to further global development of successful strategies and alternative end points for pediatric drug development in PAH.

The data that support the findings of the survey are provided in Data S1. The workshop brought together leading experts in PAH and PAH stakeholders across the globe, including regulators, researchers, clinicians, healthcare professionals, patients, and pharmaceutical industry representatives. The objectives of the workshop were to analyze the problems related to the conduct of clinical trials in children with PAH, to refine end points and study designs to address the challenges identified, and to set priorities for future research and development aspects of specific medicines as well as provide medicine developers with more advice specific to global pediatric drug development.

Current Status of Drug Development in Pediatric PAH

Randomized controlled trials have shaped advances in the care of adults with cardiovascular disease and are regarded as the gold standard design to provide evidence for regulatory approval for cardiovascular medicines. However, there are many challenges to relying exclusively on randomized clinical drug trials in adults to address the unique needs of children. Such studies cannot always be conducted in rare pediatric diseases, such as PAH. Because of these challenges, of the 9 products authorized for adults with PAH in the EU and Canada, and 11 in the United States, only 2 of these products, sildenafil and bosentan, are authorized for children in the EU and United States, respectively (Table 1). The complexity is increased in the case of the pediatric PAH population because of the many associated conditions that fragment the classification of pediatric PAH, which leaves only a relatively small number of patients with PAH at each center, facing a high number of competing medicinal products.

The lack of suitable clinical end points is another important challenge for conducting pediatric clinical trials. End points used in adults, such as the use of the 6-Minute Walking Distance (6MWD) Test, cannot be used in all pediatric age subsets. Furthermore, there is a lack of consensus about the use of right-sided heart catheterization to obtain hemodynamic end points in pediatric clinical trials. This is confounded by a lack of adequate alternative end points because of gaps in knowledge related to methods to evaluate how a child and adolescent feel and function across the age spectrum in response to therapy. These challenges have limited the use of methods commonly used in pediatric development, such as extrapolation. Methodological tools, such as extrapolation, can optimize obtaining information about children involved in clinical studies by predicting how a medicine may work in children and adolescents on the basis of studies conducted in adults.[13–15]

This situation has resulted in a lack of equipoise after marketing authorization for new investigational drugs in adults, making it even more difficult to enroll children, and contributes to off-label use, which can increase the risk of inadequate dosing and results in lack of pediatric safety data. The main points of tension are related to finding the adequate balance between early access and sufficient exposure of children during pediatric trials for safety and adequate dosing; considerations should also be given about ethical and medical aspects, particularly related to end points.

Premeeting Survey of Patients and Their Families, Healthcare Professionals, and Drug Developers on Pediatric PAH Drug Development

An online survey was conducted ahead of the workshop among all interested stakeholders to gather as much information as possible and facilitate an informed discussion. Healthcare professionals and patients in the EU, United States, and Canada were contacted as well as one expert in Japan. Survey questions were related to pathophysiological features, pharmacological behavior, mechanism of action, extrapolation, end points, quality of life, and clinical trials. Respondents included 22 healthcare professionals treating adults and children with PAH, 4 industry participants involved in PAH drug development, 26 parents of children with PAH, and 1 adolescent patient with PAH.

Table 1. Overview of Medicines Available for Use in PAH for Adults and Children

Class of Products	Product	Authorization for Adults			Authorization for Children		
		EU	United States	Canada	EU	United States	Canada
Prostacyclin analogue	Treprostinil	No	Yes	Yes	No	No	No
	Selexipag	Yes	Yes	Yes	No	No	No
	Treprostinil diethanolamine	No	Yes	No	No	No	No
	Iloprost	Yes	Yes	No	No	No	No
	Epoprostenol	Yes	Yes	Yes	No	No	No
Endothelin receptors Antagonist	Bosentan	Yes	Yes	Yes	Pharmacokinetics data	Yes	Pharmacokinetics data
	Ambrisentan	Yes	Yes	Yes	No	No	No
	Macitentan	Yes	Yes	Yes	No	No	No
Phosphodiesterase type 5 inhibitor	Sildenafil	Yes	Yes	Yes	Yes	No	No
	Tadalafil	Yes	Yes	Yes	No	No	No
Guanylate cyclase stimulators	Riociguat	Yes	Yes	Yes	No	No	No

Pediatric indications have not been granted; however, results of pharmacokinetic studies in the different pediatric age groups are summarized in the Summary of Product Characteristics, with a comparison to adults. Uncertainties caused by limited experience are also stated. EU indicates European Union; PAH, pulmonary arterial hypertension.

For the *healthcare professionals*, specific points considered central to the discussion were related to the lack of sufficient outcome measures that are applicable to young children with PAH, including the lack of established biomarkers that can predict disease risk, severity, and disease progression. Experts welcomed the opportunity to investigate the use of activity measurement for the pediatric population and acknowledged the possibility of using noninvasive techniques and candidate surrogate markers, such as selected imaging (echocardiography or cardiac magnetic resonance imaging) parameters or NT-proBNP (N-terminal pro-B-type natriuretic peptide).

With regard to *patients*, major topics for discussion were related to off-label use, end points, daily monitoring, and participation in clinical trials. Most of the patients who participated in the survey and the workshop were not concerned about the off-label use of drugs because they trust their physicians. Also, only a couple of medicinal products are licensed for children in their respective countries, leaving patients with no other choice than to accept the available therapy(-ies) even when used off label. In addition, for medicinal products already licensed for adults, patients in many countries do not have an incentive to enroll in clinical studies because they can access these medicinal products for pediatric use outside of a clinical trial.

Parents expressed concerns about the use of invasive procedures, such as right-sided heart catheterization, to obtain hemodynamic end points in clinical trials and the use of the 6MWD Test, which was not considered a good indicator of the child's health status on its own. Parents take many other variables into account to monitor the child's health status, and many are regularly monitoring oxygen saturation. The most important signs for parents that their child's health is deteriorating are an observed increase in fatigue and change in physical appearance. In addition, most of the parents were supportive of the idea to self-report specific symptoms and welcomed the possibility to gather and report data on quality of life and other important information through technologies, such as smartphone applications.

Representatives from the *pharmaceutical industry* acknowledged the challenges of conducting studies in pediatric PAH, but also welcomed clarifications about assumptions and method (eg, knowledge on appropriate end points and applicability of extrapolation) to minimize the risk of inconclusive study results. More important, the level of evidence required for licensing should not differ substantially between the different regulatory regions and stakeholders. Streamlined clinical development programs that would meet global requirements would help optimize the use of resources and achieve success in a reasonable time.

At the meeting, it was agreed that because of these various perceptions by stakeholders, pediatric development programs are disconnected from their respective adult programs. Such disconnections impede the design, recruitment, and conduct of studies in children, leading to significant delays. It is important to help ensure that the data generated in adults and children will address the scientific questions that are important for licensing for children in a timely manner.

Trial Design in Pediatric PAH: Points to Consider and Paradigm Shift

Transfer of information from the adult to the pediatric population and use of existing knowledge

Drugs approved to treat PAH in adults are typically based on a single, well-controlled clinical trial showing statistically significant improvement in exercise capacity or, more recently, improvements in a composite of mortality and morbidity end points (Table 2). The pivotal efficacy trial is usually supported by a smaller phase 2 study that relies on pharmacodynamic end points (eg, hemodynamic biomarkers obtained by right-sided heart catheterization) to show dose-response and guide selection of dosing regimens. On the basis of global requirements for the use of extrapolation,[8,15] the use of a drug in the pediatric population can be supported by adult efficacy data in 2 ways:

1. The data from the adult population support the use in pediatrics for the PAH indication. The efficacy is established in pediatric populations on the basis of an adequate and well-controlled clinical efficacy and safety trial. Efficacy in the pediatric population is assessed using an appropriate clinical end point.
2. The efficacy in the pediatric population is extrapolated from adult data. Evidence for effectiveness is based on adequate and well-controlled clinical trials in adults, with additional supporting data in the specific pediatric population, typically guided by biomarker and pharmacokinetic data. In this scenario, the pathophysiological features of some forms of PAH are proved sufficiently similar in adults and children, and there is a clear understanding of the basis for the drug's benefit (mechanism of action, ontogeny of the drug target, and disease in adults and children) and a biomarker with which to assess the drug effects in the pediatric population.

Pharmacokinetic and safety data cannot be extrapolated from adults and would need to be assessed in the pediatric population.

On the basis of the data presented at the meeting and existing knowledge at the time of the workshop, there was consensus among stakeholders that our understanding of the pathophysiological features of various PAH subgroups is still insufficient to draw detailed comparison between those seen in the adult versus the child, and consequently to extrapolate efficacy as a general rule.

A positive example in which progress has been made through adequate data collection over the past years and in which existing knowledge can translate in facilitating regulatory requirements is idiopathic PAH and some forms of associated PAH in adults and children, making progress toward extrapolation of efficacy possible. Such progress has been integrated by the Committee for Medicinal Products for

Table 2. Summary of Efficacy End Points Used to Obtain Regulatory Approval of Medicines for Use in PAH for Adults and Children

End Points Used	Study Population and Numbers of Studies	Products Approved	Limitations if Used in Pediatric Trials
Increase in 6-min walking distance[16–20]	Adults (8 studies)	Bosentan Ambrisentan Sildenafil Tadalafil Treprostinil Iloprost Epoprostenol Riociguat	• Need large sample size because of variability • Not reliable in children less than 7 y
A composite of time to the first morbidity or mortality event[21,22]	Adults (2 studies)	Macitentan Selexipag	• To further optimize and define relevant components of clinical worsening in pediatric patients with PAH • Need relatively large sample size
Increase in O_2 consumption at peak exercise via CPET[23]	Pediatrics (1 study)	Sildenafil (EU)*	51% of children were developmentally unable to perform CPET in this trial
ΔPVR/ΔPVRi assessed by RHC[24]	Pediatrics (1 study)	Bosentan (United States and Health Canada)	End points collected by invasive RHC are not supported for the purpose of pediatric trials because of ethical concerns about the risk of death and severe adverse events related to the procedure

CPET indicates cardiopulmonary exercise testing; EU, European Union; PAH, pulmonary arterial hypertension; ΔPVR, change in pulmonary vascular resistance; ΔPVRi, ΔPVR index; RHC, right-sided heart catheterization.
*Sildenafil is approved in the EU, but not in the United States and Canada, on the basis of the evidence that long-term mortality showed a dose-related adverse trend on mortality.

Human Use, which is the European Medicines Agency's committee responsible for human medicines in the pediatric addendum to its guideline on the clinical investigations of medicinal products for the treatment of PAH. Such an agreement means that there would no longer always be the necessity to run studies in which the main aim is to confirm clinical benefits, and it might not necessarily be required to conduct placebo-controlled trials. Placebo control can lead to recruitment issues, even for short-term placebo withdrawal studies, as particularly highlighted by the patient's representatives. The use of extrapolation of efficacy from adults to children could allow pediatric licensing on the basis of studies evaluating pharmacokinetics, pharmacodynamics, and safety in the pediatric population.[25] For classes of products already authorized, and with appropriate end points, adult and pediatric PAH clinical programs may proceed simultaneously, leading to timely access for children. To date, only bosentan has obtained a claim for use in the pediatric population on the basis of an extrapolation approach in the United States. During the meeting, stakeholders agreed that pharmacokinetics data alone (ie, matching blood concentrations in pediatric patients with PAH to those achieved in adult patients with PAH) would not be sufficient for extrapolation. There is the need to confirm the adequate doses with pharmacodynamics end points. Studies focusing on pharmacokinetics/pharmacodynamics may not need a control arm of another medicinal compound or placebo, but could be dose controlled with at least 3 doses to characterize the dose-response curve. Further considerations to the pharmacokinetics/pharmacodynamics study design will need to be developed, particularly paying careful attention to pediatric clinical pharmacological features early in study design, which can also help to optimize initial dose selection and data sampling.

In addition, although extrapolation might allow a reduction in the number of pediatric trial participants, it was acknowledged that extrapolation in pediatric PAH is still at a learning stage and there is a need for further data to enhance our current knowledge, specifically with respect to how developmental growth and maturation would impact pharmacokinetics/pharmacodynamics outcomes. Furthermore, efficacy data may have some residual uncertainties stemming from the limited populations and feasibility reasons at the time of initial approval. To address uncertainties at the time of marketing authorization, postauthorization studies that are performed in patient registries in which patients are recruited on the basis of a disease (ie, disease registry) rather than on the basis of a specific drug exposure can be a useful tool as they may provide robust data on disease epidemiological characteristics, patients' characteristics, and current standard of care. Conversely, experience shows that when there is the need for collaboration between registries, it is contingent on agreement on data ownership and sharing, timelines, established protocols and statistical analysis plans, consideration of methodological differences between data sources because of consideration of adequate sample size, and provision of operational and scientific support (ie, for programming and statistical analyses).[26] These pediatric-specific disease registries, such as the TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry, and, in the future, databases that accurately reflect the phenotype and genotype of neonatal and childhood PAH may prove of particular relevance to elucidate the natural history of PAH; these are critical factors that modulate outcomes and responses to therapies and related research questions. To address the need to better characterize pediatric PAH, the TOPP registry was initiated in January 2008 and is a global, prospective study designed to provide information about demographics, treatment, and outcomes in pediatric pulmonary hypertension. Furthermore, one of the tools to be considered is the model of real-world data that can help to overcome some of the challenges. However, the planning for collection of structured data is particularly important to be set up a priori with a view to be successfully implemented.

Consequently, it was agreed that the identification of the evidence necessary to inform the pediatric drug development program in pediatric PAH may require considerations for additional longitudinal systematic collection of data across developments in both adults and children, during these learning stages. The pharmaceutical industry participants considered the use of data pooling for validation of a pharmacodynamics parameter to enable extrapolation as a potential solution. For example, working across industry and sharing available placebo data or using available supportive data (eg, from other products with a similar mechanism of action, registries, or open-label data) could contribute to end point evaluation and validation.

Evidence-based medicine for pediatric PAH and end points

Regulatory approval of a drug traditionally requires demonstration that it improves a clinical outcome (ie, how a patient feels, functions, or survives) or a validated surrogate for such an outcome. Improving survival, improving exercise capacity, preventing hospitalization, and improving quality of life are all important treatment goals and have a direct impact on patients with PAH and their families. A surrogate end point is defined as an end point that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate end point does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm on the basis of epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.[27,28] At present, there are no validated surrogate end points that

can substitute for clinical end points to support traditional or accelerated approval of new therapies for pediatric PAH.

Despite emerging recent data on clinical course, prognosticators, treatment strategies, the definition of treatment targets and the potential of (surrogate) end points in pediatric PAH, clinical research in pediatric PAH has a lack of age-appropriate clinical end points, including the lack of established biomarkers that can predict disease risk, severity, and disease progression. A summary of potential useful noninvasive clinical end points is presented in Table 3. The applicability of each end point in pediatric clinical trials is described below in more detail.

Interventional clinical trials in adults have commonly used the 6MWD Test to demonstrate efficacy for drug approval; therefore, this end point could be used in pediatric patients developmentally able to perform the test.[29–31] Unfortunately, young children (aged <7 years) cannot reliably perform the test, making this a suboptimal primary end point in a study of the full age range of children. Likewise, cardiopulmonary exercise testing has failed as a primary end point in pediatric PAH sildenafil efficacy trials as 51% of children were unable to perform it.[32]

Clinical worsening as a composite end point in adult trials in PAH has incorporated certain soft components, such as need for more therapy or reductions in exercise capacity, and poses challenges in terms of interpretability in PAH.[33] Regulators have not considered the magnitude of drug effects on this end point to be of critical concern in granting such claims in adults. Thus, a program seeking such a claim in children would not need a predicate finding in adults and could be applied to forms of PAH dissimilar to those seen in adults. For instance, as shown in Table 2,[16–24] 2 recent studies in adults used a composite end point (ie, time to the first morbidity or mortality event) as the primary end point. The first morbidity or mortality events included (1) death, (2) onset of a treatment-emergent adverse event with a fatal outcome occurring within 4 weeks of study treatment discontinuation, (3) atrial septostomy or hospitalization for atrial septostomy, (4) lung transplantation or hospitalization for lung transplantation, (5) initiation of intravenous or subcutaneous prostanoids (eg, epoprostenol or treprostinil)/hospitalization for initiation of intravenous or subcutaneous prostanoids, or (6) other worsening of PAH. Such an end point could potentially be used in pediatric PAH trials to seek a claim related to disease progression in regions where such

Table 3. Noninvasive End Points With Potential Use as End Points in Clinical Trials in Children

End Point Modality	Potential Treatment Goals to be Considered	Strengths	Limitations
WHO-FC	WHO-FC improvement	• Convenience • Predictive of transplant-free survival in pediatric PAH	• Variability in classifications among clinicians • Definitions of symptoms may differ and not be reliable in children
NT-proBNP	NT-proBNP lowering	• Simple procedure (plasma) • Likely predictive of transplant-free survival in pediatric PAH prognosis	• Not a specific indicator for PAH only • Impacted by cause of PAH • The normal value of NT-proBNP in children can vary with age
Echocardiography	• TAPSE improvement • 3-Dimensional right ventricular function • Fractional area change	• Widely used for monitoring in patient population • 3-Dimensional echocardiography offers new options with end points	• High operator variability • Likely larger sample size • No consensus on which echocardiographic end point should be used as a primary outcome
Actigraphy	• Physical activity count • Heart rate variability	• Children friendly • Simple and can continuously record physical activity for days and weeks • Correlates with 6MWD Test, mPAP, and PRVi • Sensitive and, thus, potentially requires smaller sample size	• Needs to be validated in an interventional trial • Needs to optimize the cutoff values for different levels of physical activities across different devices • Seasonal and school/holiday influences
PRO	Not studied	Direct measurement of how a patient feels, functions, and survives	Not being developed

6MWD indicates 6-Minute Walking Distance; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PRO, patient-reported outcome; PVRi, pulmonary vascular resistance index; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class.

claims are explicitly written into the label.[32,34,35] A recent study in children with PAH demonstrated the feasibility of such combined end points in children and has shown that the end point components of death, lung transplantation, hospitalization, initiation of intravenous prostanoids, and functional deterioration occurred with a longitudinal event rate of 10.1, 2.5, 21.4, 9.4, and 48.1 events per 100 person-years, respectively.[36] Furthermore, it showed the soft components included in the composite were highly predictive for death or lung transplantation.

Cardiac catheterization with measurement of invasive hemodynamics and calculation of pulmonary vascular resistance, a nontherapeutic procedure, remains the *gold standard* for diagnosing PAH, evaluating disease severity, and following treatment responses in children and adults. Hemodynamic parameters have been shown to correlate with prognosis in children.[34] The US Food and Drug Administration considers pulmonary vascular resistance as a translational surrogate end point for extrapolation. The relationship between exercise capacity (measured by 6MWD Test) and pulmonary vascular resistance was developed using patient-level data from 12 placebo-controlled trials (4 drug classes, 9 drugs) of approved PAH treatments in adults. The effect of bosentan on pulmonary vascular resistance in children, as shown in one early study,[35] corresponded to a likely improvement in exercise capacity in adults and permitted the extrapolation of efficacy from adults to children with a spectrum of PAH similar to adults, and thus, to support approval of bosentan for the treatment of PAH in pediatric patients with idiopathic or congenital PAH. However, there are ethical concerns about using cardiac catheterization to obtain end points in future pediatric clinical trials.[32] Deaths and severe adverse events are reported in ≈1% to 3% of procedures during hemodynamic assessments, such as during the sildenafil pediatric trial and in registries and administrative databases.[32,37,38]

Echocardiography can provide several estimates of hemodynamic function that closely correlate with measurements obtained by right-sided heart catheterization,[39] and echocardiographic variables have been identified as predictors of outcome and are suggested as a treatment target in children with PAH.[39,40] Echocardiography, however, is subject to significant operator and interpretation variability.[41] The reliability of echocardiography has not been validated in adult interventional trials to detect treatment effect, so future randomized controlled trials could include echocardiographic variables as secondary outcomes to determine if these may be suitable surrogate end points to be used to bridge another vasodilator for PAH from adults to children.

In adults, BNP is a useful tool to assess mortality risk, progression of the disease, and response to therapy. Change in BNP measurements over time typically trend with changes in classic hemodynamic and echocardiographic parameters of disease severity for children with PAH. In the Netherlands, a national registry, and a related meta-analysis, NT-proBNP was identified as a treatment goal and prognostic factor in children.[42]

Quality of life, functional assessment, and involvement of patients

World Health Organization functional class has been used to monitor symptoms in both adults and children with PAH and is based on information on symptoms with activity and at rest, provided by the patient and/or the parents and categorized by the physician in 4 predefined classes. World Health Organization functional class is commonly used and easy to be performed in children. Although World Health Organization functional class is acceptable as a primary end point in the pediatric PAH interventional trials, this end point may require a large sample size in an interventional trial.[43,44]

Health status assessment in pediatric PAH trials could be a patient- or parent-reported outcome that directly measures how a patient feels or functions (or via parental assessment).

Patient activity could be recorded through noninvasive wearable biosensors. These need to be studied in the target population to inform patient activity measurement in study design. Actigraphy is reliably measured in adults with PAH,[45] and lower activity is linked with symptoms of fatigue and low energy and lower 6MWD Test (Spearman rank correlation=0.72, $P<0.001$).[45,46] A recent study of children 3 to 17 years old with PAH demonstrated that actigraphy is a promising candidate as an end point.[47] It is currently unknown whether actigraphy can detect treatment response in either adults or children with PAH, for what ages it might be appropriate, and exactly what parameter to use as an end point (activity counts or time spent in moderate or vigorous activity).

Areas of Consensus and Future Developments for Pediatric PAH

After 10 years since the entry into force of the EU Paediatric Medicine Regulation (EC No. 1901/2006), the number of new medicines developed for pediatric PAH continues to be insufficient. For ethical and feasibility reasons, there was agreement that there is a need to be innovative in pediatric PAH drug development programs. End points may need to be different in different age groups. All potential sources of data should be used for planning and designing drug developments, and validation should be performed. Sponsors, regulators, patients, parents, and academics should work together to ensure this happens. Industry representatives see global regulatory harmonization as a key to success and offered consideration for pooling data from registries, using open-

label data, and supporting data from approved compounds with similar mechanisms of action to facilitate the development of a common scientific approach. However, although for regulators, the geographical spread of a registry network is a key factor for understanding treatment practices and outcomes, data need to be of appropriate quality. As a future step, having tools, such as the TOPP registry, qualified for pharmacoepidemiology studies as the ECFSPR (European Cystic Fibrosis Society Patient Registry) would allow their use for regulatory purposes.[48] In addition, historically, clinical trial data have been collected in diverse data formats in independent studies. In the context of extrapolation, comparative effectiveness research, comparing the benefits and harms of interventions for clinical conditions, can accelerate pediatric development, particularly in rare disease areas. For example, the development of a set of outcomes for PAH would enable efficient data collection, data integration, and regulatory review, particularly if measured and reported, as a minimum, in all clinical trials as it would allow the reuse of clinical data.

Therefore, although the foregoing discussion addresses some of the considerations for obtaining reliable information to support use of drugs for pediatric forms of PAH, regulators remain open to discuss alternative pathways, novel end points, and novel trial designs.

Another important aspect is unique feasibility issues affecting pediatric drug development, which are related to the limited pediatric-specific resources at research centers and the scarcity of dedicated pediatric trial networks. Thus, there is the need to build these clinical trial networks to contribute to increasing patient access to trials and allow investigators to conduct multicenter and multinational trials while decreasing the time to complete a trial. To overcome some of the hurdles, it is recommended to involve all stakeholders, including patients, parents, and their organizations, as well as pediatric research networks in the conception, design, and conduct of research to improve the ethical, scientific, and clinical quality of pediatric studies.

Supported by public/private partnership, pediatric oncology is a successful example for which in the past years, because the landscape of therapeutic innovations for cancer has changed, with many more new drugs in development but with still few of them reaching children, several representatives from academic research, pharmaceutical companies, regulatory drug agencies, policy makers, as well as patient/parent advocates joined their forces and created the ACCELERATE Multistakeholder Platform in Europe.[49] The global pediatric pulmonary hypertension community, organized in the Association for Pediatric Pulmonary Hypertension and driving the multinational TOPP registry, has made already an important step in the direction toward such a network, and should follow the path set by pediatric oncology.

Acknowledgments

Additional contributors as patients and patient's representatives include Gerald and Maleen Fischer from PHA Europe, Christine Denn of the German Heart Foundation, Katherine Kroner from the Pulmonary Hypertension Association US, and Jamie Myrah of the Pulmonary Hypertension Association of Canada. Additional contributors as healthcare professionals include Stuart Rich of the Northwestern University Feinberg School of Medicine (Chicago, IL), Jean- Luc Vachiery of the Erasme Hospital, Free University of Brussels, Damien Bonnet of the Hôpital Necker Enfants Malades, Nazzareno Galie of the Alma Mater Studiorum–University of Bologna, Konstantinos Dimopoulos of Royal Brompton Hospital and Imperial College London, Shahin Moledina of the Great Ormond Street Hospital, Gerard Pons of the Hôpital Cochin Saint-Vincent de Paul, Sheila Haworth of the University College London, Hannes Sallmon of the Charité–Universitätsmedizin Berlin, Christoph Male of the Medizinische Universität Wien, Maciej Kostrubiec of the Medical University of Warsaw, Tilman Humpl and Janette T. Reyes of The Hospital for Sick Children (Toronto, ON, Canada), Ian Adatia of Glenwood Children's Heart Clinic (Edmonton, AB, Canada), Anne Fournier of the CHU (Centre Hospitalier Universitaire) Mère-Enfant Sainte-Justine (Montréal, QC, Canada), George Chandy of the Ottawa Hospital Research Institute (Ottawa, ON, Canada), Susan Richards of Stollery Children's Hospital (Edmonton, AB, Canada), Dr Shouzaburou Doi of Tokyo Medical and Dental University, and Dr Satoshi Yasukouchi of Nagano Children's Hospital of the Japan Society of Pediatric Cardiology and Cardiac Surgery. Additional contributors as industry representatives include Bruno Flamion and John Watson for the European Federation of Pharmaceutical Industries and Associations and the European Confederation of Pharmaceutical Entrepreneurs. Members of the PAH (Pulmonary Arterial Hypertension) Workshop Program Committee include some primary authors and Amany El Gazayerly (Netherlands) and Sabine Scherer and Clemens Mittmann (Germany) of the European Union Network; Andreas Kouroumalis, Andrew Thomson, Laura Fregonese, and Jan Regnstroem of the European Medicines Agency; Lynne Yao and Aliza Thompson of the US Food and Drug Administration; Allan Aizenman, Ariel Arias, Sophie-Anne Lamour, Timao Li, and Daniel Keene of Health Canada; and Krishna Prasad and Angeles Alonso of the Medicines and Healthcare Products Regulatory Agency. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

Disclosures

At the time of writing and submission of the manuscript, Ollivier was an employee of the European Medicines Agency.

References

1. Kimland E, Nydert P, Odlind V, Böttiger Y, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals—a nationwide study. *Acta Paediatr*. 2012;101:772–778.
2. Neville KA, Frattarelli DAC, Galinkin JL, Green TP, Johnson TD, Paul IM, Van Den Anker JN. Off-label use of drugs in children. *Pediatrics*. 2014;133:563–567.
3. Sachs AN, Avant D, Lee CS, Rodriguez W, Murphy MD. Pediatric information in drug product labeling. *JAMA*. 2012;307:1914.
4. European Medicines Agency. Paroxetine. Resource [internet] EMA website 2004. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/

human/referrals/Paroxetine/human_referral_000131.jsp. Accessed February 14, 2019.

5. Sun H, Vesely R, Taminiau J, Szitanyi P, Papadopoulos EJ, Isaac M, Klein A, Uzu S, Griebel D, Mulberg AE. Steps towards harmonization for clinical development of medicines in pediatric ulcerative colitis-a global scientific discussion part 1: efficacy endpoints and disease outcome assessments. *J Pediatr Gastroenterol Nutr*. 2014:58:679–683.
6. Paediatric Gaucher disease: a strategic collaborative approach from EMA and FDA. Resource [internet] European Medicines Agency website 2017. https://www.ema.europa.eu/documents/scientific-guideline/gaucher-disease-strategic-collaborative-approach-european-medicines-agency-food-drug-administration_en.pdf. Accessed February 14, 2019.
7. ICH guideline—clinical investigation of medicinal products in the pediatric population E11. Resource [internet] International Conference of Harmonisation website 2000. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf. Accessed February 14, 2019.
8. Addendum to ICH E11: clinical investigation of medicinal products in the pediatric population E11(R1). Resource [internet] International Conference of Harmonisation website 2017. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/E11-R1EWG_Step4_Addendum_2017_0818.pdf. Accessed February 14, 2019.
9. International collaboration/pediatric cluster. Resource [internet] FDA website. 2007. https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm. Accessed February 14, 2019.
10. Abman SH, Hansmann G, Archer SL, Ivy D, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj U, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037–2099.
11. Ivy DD, Abman SH, Barst RJ, Berger RM, Bonnet D, Fleming TR, Haworth SG, Raj JU, Rosenzweig EB, Schulze Neick I, Steinhorn RH, Beghetti M. Pediatric pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D117–D126.
12. EMA/FDA/Health Canada joint workshop addressing unmet needs of children with pulmonary arterial hypertension. Resource [internet] European Medicines Agency website. 2017. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/06/event_detail_001454.jsp&mid=WC0b01ac058004d5c3. Accessed February 14, 2019.
13. Final reflection paper on the use of extrapolation in the development of medicines for paediatrics. Resource [internet] European Medicines Agency website. 2018. https://www.ema.europa.eu/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf. Accessed February 14, 2019.
14. Ollivier C, Thomson A, Manolis E, Blake K, Karlsson KE, Knibbe CAJ, Pons G, Hemmings R. Commentary on the EMA Reflection Paper on the use of extrapolation in the development of medicines for paediatrics. *Br J Clin Pharmacol*. 2019;85:659–668.
15. Ollivier C, Mulugeta YL, Ruggieri L, Saint-Raymond A, Yao L. Paediatric extrapolation: a necessary paradigm shift. *Br J Clin Pharmacol*. 2019;85:675–679.
16. Gordon M. NDA 21290 bosentan, medical reviews part 1. Resource [internet] FDA website: FDA; 2001. Contract No. NDA 21290. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209279Orig1s000OtherR.pdf. Accessed February 14, 2019.
17. Gordon M. NDA 21779 iloprost clinical review: drugs. Resource [internet] FDA website: FDA; 2004. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-779_Ventavis_medr.pdf. Accessed February 14, 2019.
18. Gordon M. NDA 21845 sildenafil clinical review: drug. Resource [internet] FDA website: FDA; 2005. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM320472.pdf. Accessed February 14, 2019.
19. Preston M, Dunnmon M. NDA 2048119 riociguat clinical review: drugs. Resource [internet] FDA website: FDA; 2013. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204819Orig1s000MedR.pdf. Accessed February 14, 2019.
20. Marciniak TA, Liu Q, Stockbridge N. NDA 22-081 ambrissentan, clinical and statistical review: drugs. Resource [internet] FDA website: FDA; 2007. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022081s000_MedR_P1.pdf. Accessed February 14, 2019.
21. Southworth MRP. NDA 204410 macitentan cross-discipline team leader review: drugs. Resource [internet] FDA website: FDA; 2013. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000SumR.pdf. Accessed February 14, 2019.
22. Gordon M. NDA 207947 selexipag clinical review: drugs. Resource [internet] FDA website: FDA; 2015. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207947Orig1s000MedR.pdf. Accessed February 14, 2019.
23. Gordon M. NDA 203109 sildenafil clinical review (pediatric): drugs. Resource [internet] FDA website: FDA; 2012. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM320472.pdf. Accessed February 14, 2019.
24. Chirstine Garnett PJF. NDA 209279 bosentan clinical and clinical pharmacology efficacy review (pediatrics): drugs. Resource [internet] FDA website: FDA; 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209279Orig1s000SumR.pdf. Accessed February 14, 2019.
25. Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension. Resource [internet] European Medicines Agency website. 2011. https://www.ema.europa.eu/documents/scientific-guideline/paediatric-addendum-committee-medicinal-products-human-use-guideline-clinical-investigations_en.pdf. Accessed February 14, 2019.
26. EMA Patient Registries Workshop, 28 October 2016—observations and recommendations arising from the workshop. Resource [internet] European Medicines Agency website 2017. https://www.ema.europa.eu/documents/report/report-patient-registries-workshop_en.pdf. Accessed February 14, 2019.
27. Robb MA, McInnes PM, Califf RM. Biomarkers and surrogate endpoints: developing common terminology and definitions. *JAMA*. 2016;315:1107.
28. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools). Resource [internet] FDA website: FDA; 2016. https://www.ncbi.nlm.nih.gov/books/NBK326791/copublished by National Institutes of Health (US), Bethesda, MD. Accessed February 14, 2019.
29. Douwes JM, Hegeman AK, van der Krieke MB, Roofthooft MTR, Hillege HL, Berger RMF. Six-minute walking distance and decrease in oxygen saturation during the six-minute walk test in pediatric pulmonary arterial hypertension. *Int J Cardiol*. 2016;202:34–39.
30. Douwes JM, Roofthooft MTR, Van Loon RLE, Ploegstra M-J, Bartelds B, Hillege HL, Berger R. Sildenafil add-on therapy in paediatric pulmonary arterial hypertension, experiences of a national referral centre. *Heart*. 2014;100:224–230.
31. Zuk M, Migdal A, Jagiellowicz-Kowalska D, Mazurkiewicz K, Sadel-Wieczorek A, Brzezinska-Rajszys G. Six-minute walk test in evaluation of children with pulmonary arterial hypertension. *Pediatr Cardiol*. 2017;38:754–761.
32. Sun H, Stockbridge N, Ariagno RL, Murphy D, Nelson RM, Rodriguez W. Reliable and developmentally appropriate study end points are needed to achieve drug development for treatment of pediatric pulmonary arterial hypertension. *J Perinatol*. 2016;36:1029–1033.
33. Ventetuolo CE, Benza RL, Peacock AJ, Zamanian RT, Badesch DB, Kawut SM. Surrogate and combined end points in pulmonary arterial hypertension. *Proc Am Thorac Soc*. 2008;5:617–622.
34. Ploegstra M-J, Zijlstra WMH, Douwes JM, Hillege HL, Berger RMF. Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. *Int J Cardiol*. 2015;184:198–207.
35. Barst R, Ivy D, Dingemanse J, Widlitz A, Schmitt K, van Giersbergen P. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther*. 2003;73:372–382.
36. Ploegstra M-J, Arjaans S, Zijlstra WMH, Douwes JM, Vissia-Kazemier TR, Roofthooft MTR, Hillege HL, Berger RMF. Clinical worsening as composite study end point in pediatric pulmonary arterial hypertension. *Chest*. 2015;148:655–666.
37. Beghetti M, Schulze-Neick I, Berger RMF, Ivy DD, Bonnet D, Weintraub RG, Saji T, Yung D, Mallory GB, Geiger R, Berger JT, Barst RJ, Humpl T, Mattos S, Jing ZC, Han ZY, Sondergaard L, Jensen T, Levy M, Mebus S, Apitz CH, Szatmari A, Ablonczy L, Milanesi O, Favero V, Pulido T, De La Garza P, Douwes JM, Brun H, Moll L, Michalak K, Kawalec W, Zuk M, Fasnacht Boillat M, Olgunturk R, Serdar Kula S, Alehan D, Day RW, Austin E, Moore DJ, Atz AM, Feinstein JA; TOPP Investigators. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: insights from the Global TOPP Registry (tracking outcomes and practice in paediatric pulmonary hypertension). *Int J Cardiol*. 2016;203:325–330.
38. O'Byrne ML, Glatz AC, Hanna BD, Shinohara RT, Gillespie MJ, Dori Y, Rome JJ, Kawut SM. Predictors of catastrophic adverse outcomes in children with pulmonary hypertension undergoing cardiac catheterization. *J Am Coll Cardiol*. 2015;66:1261–1269.
39. Colvin KL, Dufva MJ, Delaney RP, Ivy DD, Stenmark KR, Yeager ME. Biomarkers for pediatric pulmonary arterial hypertension—a call to collaborate. *Front Pediatr*. 2014;2:7.

40. Jone P-N, Ivy DD. Echocardiography in pediatric pulmonary hypertension. *Front Pediatr*. 2014;2:124.
41. Humbert M, Gerry Coghlan J, Khanna D. Early detection and management of pulmonary arterial hypertension. *Eur Respir Rev*. 2012;21:306–312.
42. Ploegstra M-J, Douwes JM, Roofthooft MTR, Zijlstra WMH, Hillege HL, Berger RMF. Identification of treatment goals in paediatric pulmonary arterial hypertension. *Eur Respir J*. 2014;44:1616–1626.
43. Taichman DB, McGoon MD, Harhay MO, Archer-Chicko C, Sager JS, Murugappan M, Chakinali MM, Palevsky HI, Gallop R. Wide variation in clinicians' assessment of New York Heart Association/World Health Organization functional class in patients with pulmonary arterial hypertension. *Mayo Clin Proc*. 2009;84:586–592.
44. Hassoun PM, Nikkho S, Oudiz RJ. Updating clinical endpoints in pulmonary arterial hypertension: when challenges are welcome. *Pulm Circ*. 2013;3:721–722.
45. Matura LA, Shou H, Fritz JS, Smith KA, Vaidya A, Pinder D, Archer-Chicko C, Dubow D, Palevsky HI, Sommers MS, Kawut SM. Physical activity and symptoms in pulmonary arterial hypertension. *Chest*. 2016;150:46–56.
46. Pugh ME, Buchowski MS, Robbins IM, Newman JH, Hemnes AR. Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. *Chest*. 2012;142:1391–1398.
47. Zijlstra WMH, Ploegstra M-J, Vissia-Kazemier T, Roofthooft MTR, Sarvaas GDM, Bartelds B, Rackowitz A, van den Heuvel F, Hillege HL, Plasqui G, Berger RMF. Physical activity in pediatric pulmonary arterial hypertension measured by accelerometry: a candidate clinical endpoint. *Am J Respir Crit Care Med*. 2017;196:220–227.
48. CHMP qualification procedure. Resource [internet] European Medicines Agency website. 2018. https://www.ema.europa.eu/documents/regulatory-procedural-guideline/qualification-opinion-european-cystic-fibrosis-society-patient-registry-ecfspr-cf-pharmaco_en.pdf. Accessed February 14, 2019.
49. Vassal G, Rousseau R, Blanc P, Moreno L, Bode G, Schwoch S, Schrappe M, Skolnik J, Bergman L, Bradley-Garelik MB, Saha V, Pearson A, Zwierzina H. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. *Eur J Cancer*. 2015;51:218–224.

Key Words: patient-reported outcome • pediatrics • pharmacology • research ethics • research method